REMARKS

The Office Action of July 28, 2004 presents the examination of claims 1-94 and 96-143. These claims are canceled, being replaced by the present claims 144-215. This method of amendment was chosen for its editorial simplicity.

Support for the new claims

The present claims are directed to the subject matter of the prior claims1-94 and 96-143. In general, the recitations of the claims are similar to those of the original claims. The present claims are organized as a set directed to recombinant vectors as isolated polynucleotides, chimeric viruses, and an immunogenic composition comprising one of those viruses, and methods for making the viruses by expression of one of the recombinant vectors.

The new independent claims 144, 146 and 147 recite an isolated polynucleotide comprising in operable linkage i) a transcriptional promoter active in a mammalian cell or in vitro, ii) a polynucleotide encoding a human partial or complete PIV genome or antigenome and comprising at least one of a set of selected sequences specified by SEQ ID NO. and iii) a transcriptional promoter active in a mammalian cell or in vitro. Support for the arrangement of the elements of the transcription vector is found, e.g. at page 19, lines 5-36. Support for the particular sequence listed in the claim is found at Table 8 at p. 92.

The new independent claim 148 describes an isolated polynucleotide encoding a chimeric partial or complete PIV genome or antigenome that provides a phenotype of at least 10-fold attenuation in the respiratory tract of a subject infected with a virus comprising such a genome, the chimeric genome or antigenome including background partial or complete PIV genome and at least one heterologous PIV sequence, and further including a gene encoding a wild-type L protein of either the background PIV or the heterologous PIV. This embodiment finds support in the specification at, e.g. the data in Table 11 at p. 102 (except perhaps the M protein or HN protein alone) and the paragraph following. See also, Figure 19B. A "background" PIV is described at page 40, lines 20-21.

A "partial or complete PIV genome" is described e.g. at page 19, lines 15-18. This text describes that the genome or antigenome of the virus need only contain genes or portions thereof

necessary to produce infectious particles, which may be viral or sub-viral (i.e. containing less than all of the viral proteins) particles. Of course several embodiments in which a complete viral genome are used are described, e.g. in the description of the Figures 8-10 at page 14, lines 18-19.

Claim 149 recites specific mutations that are further included in the chimeric genome or antigenome. This list of mutations is found at page 28, line 10 to page 29, line 13.

Claims 150-158 and 161-165 recite that one or both of the HN and F glycoprotein open reading frames are from the heterologous PIV, which may be HPIV1. Such a construct is illustrated in Figure 19 and is described further at page 35, lines 1-9.

Claim 159 describes a chimeric HN or G glycoprotein gene, such as described at page 37, lines 13-21.

Independent claim 160 recites that the chimeric genome or antigenome comprises at least one point mutation that confers a phenotype of at least 10-fold attenuation in the respiratory tract of a subject infected with a virus comprising such a genome or antigenome, and that the chimeric genome or antigenome also encodes a wild-type L protein of the background or heterologous PIV. Support for claim 160 is found, e.g. in the data in Table 11, at page 102 and the paragraph following.

Independent claim 166 recites that the chimeric genome or antigenome comprises a heterologous polynucleotide sequence that is part of a transcription unit having an open reading frame from a heterologous PIV and gene start (GS) and gene end (GE) sequences from the background partial or complete PIV genome or antigenome. This emodiment is supported by disclosure at, e.g., p. 26, lines 10-14 ("such as promoters... and transcription signals, can also be routinely manipulated...") with Example II and Figure 3 showing insertion of CAT between background GS and GE sequences. See also Page 25, lines 23-26 ("Mutations can vary from single nucleotide changes to ... replacement of ... genome segments. Genome segments can correspond to structural ... domains") and page 37, lines 35-37 ("The replacement of a human PIV coding sequence or non-coding sequence..."). A "transcription unit" is described at page 13, lines 29-36.

Replacement of an open reading frame in the background genome or antigenome (claim 167) or addition of another transcription unit (claim 168) is described, e.g. at page 40, line 12-14 ("... individual genes or gene segments ... are replaced or supplemented with counterpart genes or gene segments....")

The list of point mutations in claims 169 and 170 are presented at page 28, line 10 to page 29, line 13. The list of sequences incorporated in claims 171-173 is described in Table 8 at p. 92

Claims 174-176 recite that the chimeric genome includes an open reading frame of a heterologous HN or F gene or both that may be of HPIV1. This embodiment is illustrated at Figures 14, 15A and described at p. 16, lines 1 ff.

The corresponding claims to chimeric viruses, immunogenic compositions and methods for making the viruses are similarly supported.

Substance of the Interview

A personal interview with the Examiner and her Supervisor was held on July 13, 2005 and a further telephone discussion with the Examiner was held later that day. Applicants wish to thank the Examiner and her Supervisor very much for providing so much of their time to help resolve the issues in this matter.

Applicants first addressed the Collins and Klein references of record in other applications. That discussion is addressed in responses in which it is relevant.

Applicants presented proposed claim amendments that were considered by the Examiner and further explained how the amended claims were patentable over the Belshe reference (US 5,869,036). The Examiner or her supervisor provided some comment upon the proposed claims, such comments generally being limited to suggestions for avoiding possible rejections for lack of written description. It was acknowledged that Applicants' proposed claims, which are reflected in the claims presented in this paper and include the suggestions of the Examiner or her Supervisor, would likely be considered to distinguish the invention over Belshe.

The Examiner also agreed that claims to embodiments of chimeric viruses, immunogenic compositions comprising such viruses, isolated polynucleotides constituting the genomes of such viruses, expression vectors constituting such polynucleotides, methods for making the chimeric viruses, and methods for immunization using the viruses, would all be examined in the present application if presented.

The possibility of restriction of examination to one of the various listed sequences in claims 144-148 and 179-183 (and in dependent claims 171-173 and 206-208) was also discussed. Applicants pointed out that the listed sequences represented specific instances of mutations more broadly claimed at the amino acid level in the previously pending, already examined claims. The Examiner agreed that, in view of this fact, and the fact that the listed sequences are of short length, restriction would not likely be imposed at this time.

Issues raised in the Office Action

Claims 1-17, 20, 21, 26, 27, 30, 33-41, 43-50, 52, 54-59, 61-94, 96-116, 118 and 1120-143 are rejected under 35 U.S.C. § 102(e) or alternatively under 35 U.S.C. § 103(a) as being anticipated by or obvious in view of Belshe et al. U.S. 5,869,036. Claims 18, 19, 28 and 29 are rejected under 35 U.S.C. § 102(e), or alternatively under 35 U.S.C. § 103(a) as anticipated by or obvious over Belshe in view of Stokes et al (*Virus Research* 1993). Claims 22-25, 31, 32, 42, 60, 117 and 119 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Conzelmann (*J. Gen. Virol.* 1996).

Claims 91-143 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-67 of copending application 10/030,544.

All of the above rejections are moot in view of the substitution of the present claims 144-215 for the prior claims 1-143. Applicants submit that the above-stated rejections should not be applied against the present claims 144-215.

Rejections for double patenting

The 10/030,544 application has been abandoned, rendering the obviousness-type double patenting rejection moot. However, Continuation Applications claiming priority of the '544 application have been filed.

Applicants take due note that several copending applications are provisionally rejected over the claims of one another. Applicants note the ongoing nature of the prosecution of the set of copending applications, including amendment of the present claims, and submit that these rejections should be held in abeyance until at least one of the co-pending applications is allowed. Applicants will address any obviousness-type double patenting issues in an appropriate fashion in any particular application once one or more of the group of copending applications is allowed.

Rejection for anticipation and/or obviousness

As to the Belshe reference, Applicants have previously argued that Belshe '036 is not enabling of its disclosed embodiments and Applicants maintain their view that such is the case. However, the USPTO has made clear, in this and other applications of the Applicants, their position that concession that Belshe is not enabling of its disclosure includes an admission that the reference does not enable its claims and would therefore be invalid and that such a finding will not be made without intercession of the Board of Appeals or other higher authority than the Examining Corps.

Thus, to advance prosecution of the present application, Applicants have presented new claims that make more clear the distinctions between the present invention and what is disclosed or suggested by Belshe.

The entirety of the Belshe '036 patent relies upon extrapolation from a single kind of experiment. That is, all of Belshe's speculation comes from the result of experiments in which growth of a cp45 strain of HPIV3 at various temperatures is complemented by a plasmid expressing one or more of the NP, P and L protein of the wild-type HPIV3. This experiment is summarized in the attached Exhibit 1.

HPIV3 strain cp45 was known to exhibit a temperature sensitive phenotype for replication, such that, at 39.5 °C, the replication of the virus is nil (see Table 1 at col. 6).

Complementation by a plasmid expressing wild-type HPIV3 L protein provides some very small degree of recovery of virus plaques at the non-permissive temperature; about 300 or so plaques were formed, in comparison with the yield of 8×10^6 seen for the wild-type HPIV3 (compare Table 3 at col. 8 with Table 1 at col. 6).

Belshe concluded that the temperature sensitive replication phenotype of the cp45 virus was due to mutations in the L protein. From this single conclusion, Belshe et al. speculate about how a recombinant virus can be constructed.

Applicants have previously argued strenuously that Belshe does not establish any kind of expectation of success in making the "hybrid" viruses that he describes or in making the present invention. However, as to the present claims, the Examiner should consider a few things about the Belshe reference.

First, the only genome described by Belshe et al. is a non-recombinant genome of the cp45 strain. Belshe et al. do not describe any sort of recombinant genome; they mention at col. 9, lines 64-66 that Example 7 "details methods for producing attenuated hybrid vaccines for target viruses...". However, Example 7 only provides citations of papers that describe the nucleic acid sequences of various viral genes. Belshe does state at the bottom of col. 8 that, "The gene sequence which encodes the surface glycoproteins of a target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result in a hybrid virus." However, there is no further description of how this might be accomplished. At col. 9, lines 6-19, Belshe et al. describe that a hybrid virus should contain the 3' leader of cp45, NP, P[+C] and M proteins of cp45, a sequence encoding at least one surface glycoprotein of "an enveloped target virus" and "a variant protein which is different from the L protein of wild-type HPIV 3." All of the remaining disclosure of Belshe emphasizes that the L protein of any hybrid virus must be a variant from the wild-type L protein of cp45.

At the bottom of col. 6, Belshe et al. state that changes in the neuraminidase protein provide only minor decreases in replication, by less than a factor of 10, and therefore this protein is not a major factor in the attenuation of cp45. Belshe et al. also note that perhaps changes in the 3' leader sequence are "suspected in affecting the cold adaptive, temperature sensitivity and/or attenuation phenotypes of cp45." Thus, the only significant mechanism of attenuation

that Belshe discloses or suggests is mutation of the L protein to a temperature sensitive phenotype by one or more point mutations.

To summarize, Belshe et al. only describe use of a cp45 genome or antigenome, having at least two of three defined point mutations in the L protein, to obtain an attenuated HPIV3 virus. The cp45 genome is a genome of a HPIV strain. Mutation of the L protein, and perhaps (though not definitively) in the 3' leader sequence, is the only mechanism of attenuation disclosed or suggested. Belshe et al. suggest that such an attenuated HPIV3 virus might be modified by substitution of its genes encoding the HN and/or F glycoproteins with the corresponding genes from a "target virus" among those listed at col. 8, lines 42-58. However, as explained above, and in painstaking detail previously, Belshe et al. provide no disclosure whatsoever about how to accomplish such substitution.

On the other hand, except for claims 144-147 (and corresponding virus claims), the present claims recite that a chimeric genome is formed by mixing genes from different PIV viruses to obtain an attenuated chimeric virus. The claims recite a threshold level of attenuation that is obtained *in vivo* and that is achieved despite the presence of a gene encoding wild-type L protein in the genome (claims 148 and 160, claims 184 and 195, and claims dependent therefrom). Thus, Belshe et al. do not disclose or suggest the instant invention. In fact, Belshe et al. teach away from the invention so claimed. Accordingly, the present claims 148-165, 184-200, and 214, 215 as dependent thereon are both novel and unobvious over Belshe et al.

Claims 114-147 (and 214, 215 as dependent thereon) recite specific nucleotide sequences, which encode the individual point mutations found in HPIV3cp45, to be incorporated into a recombinant partial or complete PIV genome or antigenome. Applicants submit that Belshe et al. do not disclose or suggest that any one (claims 144 and 179) or that all but three of these sequences (claims 146, 147 and 181-182) should be incorporated into a partial or complete PIV genome or antigenome. Belshe et al. do not contemplate the introduction or removal of any restriction site marker (accomplished by selection of particular codons for encoding the mutation), nor that two nucleotides of a codon should be mutated to stabilize the mutation against reversion (SEQ ID Nos: 10 and 15). Finally, Applicants especially note that Belshe does not at all contemplate any attenuated virus obtained by mutating other than the L protein.

Finally, as to claims 166-178 and 201-213 (and 214, 215 as dependent thereon), these claims recite that the chimeric genome or antigenome comprises a heterologous transcription unit in which the open reading frame portion of a heterologous gene is inserted between the GS and GE sequences of the background PIV. Belshe et al. provide no concept whatsoever related to this embodiment of the invention. Accordingly, claims 166-178, 201-213 and 214, 215 as dependent thereon should be found novel and unobvious over Belshe et al.

Conzelmann presents a review of the progress in genetic manipulation of the non-segmented, negative strand RNA viruses. Conzelmann describes a basic rescue system for such viral genomes. However, like Belshe et al., Conzelmann does not describe or suggest any of the ways to create an attenuated virus that are recited in the present claims. That is, Conzelmann does not describe or suggest that making a chimeric genome that includes a wild-type L protein, or introducing any particular point mutations, would produce a virus that is at least 10-fold attenuated in the respiratory tract of an infected host. Neither does Conzelmann suggest the specific sequences listed in Table 8 or insertion of an open reading frame of a protein between the GS and GE sequences of a background virus. Thus, combining Conzelmann with Belshe et al. fails to remedy the deficiency of Belshe alone in establishing *prima facie* obviousness of the present claims.

Stokes et al. describe the characterization of the "biologically derived" HPIV3 strain cp45. This strain was derived from wild-type HPIV3 JS by cold passaging the virus in culture. Stokes et al. identify 18 point mutations in the viral genome. The HPIV3 cp45 virus exhibits an attenuated phenotype *in vivo*.

Stokes et al. do not describe the contribution of any particular mutation to the attenuation phenotype. In regard to the particular nucleotide sequences recited in claims 144-148 and 179-182, the nucleotide sequences described or suggested by Stokes et al. are not among the sequences listed in claims 144-148 and 179-182. Neither the mutation at nucleotide 40 of the leader sequence nor any N protein mutations are indicated, and the remaining nucleotide sequences listed in Table 8 include at least one point mutation distinct from or in addition to the one indicated by Stokes et al. in their Figure 2.

Thus, with respect to claims 144-148 and 179-182, Stokes et al. either do not disclose or suggest a feature of the invention, or the reference fails to provide any motivation to make the recited invention. The latter is especially true in view of the Belshe reference, which points one of ordinary skill in the art in the direction of making mutations in the L protein to achieve an attenuation phenotype. At best, these combined references make it "obvious to try" to make the embodiment having a mutation in the 3' leader sequence at nucleotides 23 and 28 (SEQ ID NOs: 47 and 48) in order to test whether these mutations would create an attenuation phenotype, but such is not sufficient to establish *prima facie* obviousness of the invention of claims 144-148 and 179-182 (and 214, 215 as dependent thereon).

As to the remaining claims, Stokes et al. do not describe or suggest that making a chimeric genome that includes a wild-type L protein, would produce a virus that is at least 10-fold attenuated in the respiratory tract of an infected host. Neither do Stokes et al. disclose or suggest insertion of an open reading frame of a protein between the GS and GE sequences of a background virus. Thus, combining Stokes et al. with Conzelmann and Belshe et al. fails to remedy the deficiency of Belshe alone, or of Belshe combined with Conzelmann, in establishing *prima facie* obviousness of claims 149-178 and 183-213 (and 214, 215 as dependent thereon).

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

By _____

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